

ELECTRONIC SUPPLEMENTARY MATERIAL

Drugs – Real World Outcomes

Real-World Amount of Clotting Factor Products and Non-Factor Products Dispensed and Annual Medical Expenditures for Japanese Patients with Hemophilia A

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Table S1 Observed treatment duration and annualized dosage of treatment for hemophilia A by age category in outpatients

	SHL/plasma-derived products						EHL products			
	Lonoctocog alfa (n = 12)	Octocog alfa (n = 190)	Octocog beta (n = 217)	Rurioctocog alfa (n = 392)	Turoctocog alfa (n = 36)	pdFVIII (n = 86)	Damoctocog alfa pegol (n = 36)	Efraloctocog alfa (n = 230)	Rurioctocog alfa pegol (n = 192)	Turoctocog alfa pegol (n = 2)
Age 0–11 years										
	n = 0	n = 32	n = 33	n = 117	n = 3	n = 3	n = 0	n = 59	n = 38	n = 1
Annualized FVIII dosage, median, IU/kg (Q1–Q3)	–	n = 35 3919.0 (3019.8– 5723.6)	n = 37 3565.8 (1246.6– 5074.2)	n = 138 3764.5 (1421.0– 7025.2)	n = 3 2418.8 (1336.5– 5601.7)	n = 3 467.9 (296.5– 6124.5)	–	n = 86 4120.7 (1087.2– 5089.4)	n = 50 4974.5 (3163.6– 6355.2)	n = 1 7838.2 (7838.2– 7838.2)
Observed treatment duration, n (%)	n = 0	n = 35	n = 38	n = 139	n = 3	n = 3	n = 0	n = 86	n = 51	n = 1
<6 months	0	2 (5.7)	8 (21.1)	38 (27.3)	0	1 (33.3)	0	30 (34.9)	20 (39.2)	0
6 to <12 months	0	1 (2.9)	4 (10.5)	13 (9.4)	0	0	0	11 (12.8)	12 (23.5)	1 (100)
1 to <2 years	0	20 (57.1)	8 (21.1)	20 (14.4)	1 (33.3)	1 (33.3)	0	16 (18.6)	12 (23.5)	0
2 to <3 years	0	7 (20.0)	8 (21.1)	20 (14.4)	1 (33.3)	0	0	16 (18.6)	7 (13.7)	0
≥3 years	0	5 (14.3)	10 (26.3)	48 (34.5)	1 (33.3)	1 (33.3)	0	13 (15.1)	0	0
Age 12–19 years										
	n = 2	n = 30	n = 31	n = 55	n = 11	n = 6	n = 1	n = 24	n = 19	n = 0
Annualized FVIII dosage, median, IU/kg (Q1–Q3)	n = 3 5725.8 (206.5– 6432.0)	n = 32 4132.6 (2183.9– 5252.1)	n = 35 3801.9 (1680.4– 4698.2)	n = 58 2954.8 (1011.3– 4806.9)	n = 11 4840.1 (3643.2– 5498.4)	n = 7 1705.3 (204.1– 4928.7)	n = 1 3420.4 (3420.4– 3420.4)	n = 27 3515.1 (1808.5– 4865.7)	n = 19 3412.9 (2133.9– 4587.8)	–
Observed treatment duration, n (%)	n = 3	n = 32	n = 36	n = 58	n = 11	n = 7	n = 1	n = 28	n = 20	n = 0
<6 months	0	6 (18.8)	9 (25.0)	9 (15.5)	1 (9.1)	2 (28.6)	0	6 (21.4)	6 (30.0)	0
6 to <12 months	2 (66.7)	2 (6.3)	2 (5.6)	7 (12.1)	2 (18.2)	1 (14.3)	0	2 (7.1)	2 (10.0)	0
1 to <2 years	1 (33.3)	13 (40.6)	13 (36.1)	8 (13.8)	1 (9.1)	0	1 (100)	5 (17.9)	6 (30.0)	0
2 to <3 years	0	8 (25.0)	3 (8.3)	17 (29.3)	3 (27.3)	0	0	6 (21.4)	6 (30.0)	0
≥3 years	0	3 (9.4)	9 (25.0)	17 (29.3)	4 (36.4)	4 (57.1)	0	9 (32.1)	0	0

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	Lonoctocog alfa (<i>n</i> = 12)	Octocog alfa (<i>n</i> = 190)	Octocog beta (<i>n</i> = 217)	Rurioctocog alfa (<i>n</i> = 392)	Turoctocog alfa (<i>n</i> = 36)	pdFVIII (<i>n</i> = 86)	Damoctocog alfa pegol (<i>n</i> = 36)	Efraloctocog alfa (<i>n</i> = 230)	Rurioctocog alfa pegol (<i>n</i> = 192)	Turoctocog alfa pegol (<i>n</i> = 2)
Age 20–64 years										
	<i>n</i> = 9	<i>n</i> = 119	<i>n</i> = 146	<i>n</i> = 201	<i>n</i> = 17	<i>n</i> = 63	<i>n</i> = 33	<i>n</i> = 137	<i>n</i> = 119	<i>n</i> = 0
Annualized FVIII dosage, median, IU/kg (Q1–Q3)										
	<i>n</i> = 9	<i>n</i> = 124	<i>n</i> = 177	<i>n</i> = 235	<i>n</i> = 18	<i>n</i> = 65	<i>n</i> = 35	<i>n</i> = 217	<i>n</i> = 139	–
	4589.1	1954.6	1734.1	1524.7	5383.3	1226.0	2850.0	2173.9	2738.1	
	(1732.9–	(1008.7–	(851.7–	(736.0–	(2135.5–	(369.8–	(2197.0–	(866.5–	(1414.0–	
	5146.5)	2964.3)	3274.2)	3256.4)	7686.1)	2791.7)	3749.2)	3524.6)	3847.1)	
Observed treatment duration, <i>n</i> (%)										
	<i>n</i> = 9	<i>n</i> = 124	<i>n</i> = 184	<i>n</i> = 237	<i>n</i> = 18	<i>n</i> = 67	<i>n</i> = 38	<i>n</i> = 229	<i>n</i> = 145	<i>n</i> = 0
<6 months	1 (11.1)	23 (18.6)	52 (28.3)	50 (21.1)	3 (16.7)	9 (13.4)	17 (44.7)	95 (41.5)	38 (26.2)	0
6 to <12 months	3 (33.3)	17 (13.7)	20 (10.9)	27 (11.4)	1 (5.6)	3 (4.5)	20 (52.6)	18 (7.9)	23 (15.9)	0
1 to <2 years	4 (44.4)	42 (33.9)	30 (16.3)	51 (21.5)	4 (22.2)	13 (19.4)	1 (2.6)	22 (9.6)	69 (47.6)	0
2 to <3 years	1 (11.1)	22 (17.7)	50 (27.2)	53 (22.4)	7 (38.9)	11 (16.4)	0	29 (12.7)	15 (10.3)	0
≥3 years	0	20 (16.1)	32 (17.4)	56 (23.6)	3 (16.7)	31 (46.3)	0	65 (28.4)	0	0
Age ≥65 years										
	<i>n</i> = 1	<i>n</i> = 10	<i>n</i> = 11	<i>n</i> = 23	<i>n</i> = 5	<i>n</i> = 14	<i>n</i> = 3	<i>n</i> = 13	<i>n</i> = 16	<i>n</i> = 1
Annualized FVIII dosage, median, IU/kg (Q1–Q3)										
	<i>n</i> = 1	<i>n</i> = 12	<i>n</i> = 11	<i>n</i> = 27	<i>n</i> = 12	<i>n</i> = 14	<i>n</i> = 6	<i>n</i> = 27	<i>n</i> = 18	<i>n</i> = 2
	2383.3	226.7	1149.4	880.5	2262.0	444.2	3091.1	1000.4	1755.5	2178.3
	(2383.3–	(113.4–	(385.2–	(278.3–	(1826.8–	(223.6–	(2610.7–	(388.5–	(1061.5–	(2167.5–
	2383.3)	1952.0)	3132.5)	1656.8)	4113.4)	1247.1)	3319.3)	2164.6)	3706.8)	2189.1)
Observed treatment duration, <i>n</i> (%)										
	<i>n</i> = 1	<i>n</i> = 12	<i>n</i> = 11	<i>n</i> = 27	<i>n</i> = 12	<i>n</i> = 14	<i>n</i> = 7	<i>n</i> = 29	<i>n</i> = 22	<i>n</i> = 2
<6 months	0	4 (33.3)	4 (36.4)	8 (29.6)	6 (50.0)	3 (21.4)	6 (85.7)	19 (65.5)	12 (54.6)	1 (50.0)
6 to <12 months	1 (100.0)	1 (8.3)	1 (9.1)	1 (3.7)	2 (16.7)	1 (7.1)	1 (14.3)	2 (6.9)	2 (9.1)	1 (50.0)
1 to <2 years	0	3 (25.0)	0	3 (11.1)	3 (25.0)	6 (42.9)	0	2 (6.9)	7 (31.8)	0
2 to <3 years	0	2 (16.7)	2 (18.2)	7 (25.9)	0	1 (7.1)	0	4 (13.8)	1 (4.6)	0
≥3 years	0	2 (16.7)	4 (36.4)	8 (29.6)	1 (8.3)	3(21.4)	0	2 (6.9)	0	0

EHL extended half-life, *FVIII* factor VIII, *Q* quartile, *SHL* standard half-life

The *n* in the column heading is the number of unique patients that used the specified treatment. The *n* in the rows for annualized FVIII dosage and treatment duration is larger as an individual patient may have used a specified treatment multiple times at different time points.

Table S2 Prevalence of joint damage, by age group

	Aged 0–11 years (<i>n</i> = 207)	Aged 12–19 years (<i>n</i> = 126)	Aged 20–64 years (<i>n</i> = 573)	Aged ≥65 years (<i>n</i> = 68)
Patients with joint damage, <i>n</i> (%)	105 (50.7)	64 (50.8)	336 (58.6)	41 (60.3)

Table S3 Mean (SD) and median (Q1–Q3) annual medical expenditures in yen in patients receiving regular treatment for hemophilia A, by age group

Expenditure type	Overall	2016	2017	2018	2019	2020
Aged 0–11 years						
Annual expenditures for CFC and emicizumab treatment	<i>n</i> = 176 8,932,523.7 (5,741,097.6) 8,777,190 (4,894,001–11,912,050)	<i>n</i> = 106 6,147,098.8 (4,616,877.3) 5,505,396 (2,199,382–9,041,263)	<i>n</i> = 142 7,322,689.0 (5,167,606.6) 7,000,630 (3,195,660–11,244,596)	<i>n</i> = 152 8,129,327.3 (5,832,302.7) 7,264,882 (3,512,754–11,787,254)	<i>n</i> = 157 11,365,387 (8,179,350.7) 10,650,079 (6,205,424–14,954,092)	<i>n</i> = 134 13,736,128 (10,404,538) 12,491,590 (6,821,022–17,011,378)
Annual expenditures for CFC treatment	<i>n</i> = 168 7,653,174.6 (5,205,884.4) 7,173,499 (3,653,147–11,133,264)	<i>n</i> = 106 6,147,098.8 (4,616,877.3) 5,505,396 (2,199,382–9,041,263)	<i>n</i> = 142 7,322,689.0 (5,167,606.6) 7,000,630 (3,195,660–11,244,596)	<i>n</i> = 151 8,180,458.1 (5,817,430.2) 7,333,380 (3,556,534–11,824,995)	<i>n</i> = 146 9,314,424.7 (6,499,683.2) 8,951,671 (4,300,898–13,743,630)	<i>n</i> = 108 10,782,786 (7,685,573.8) 9,846,955 (4,732,547–15,214,649)
Annual expenditures for emicizumab treatment	<i>n</i> = 26 16,495,386 (10,290,742) 13,915,860 (10,216,591–17,206,714)	<i>n</i> = 0 – –	<i>n</i> = 0 – –	<i>n</i> = 0 – –	<i>n</i> = 26 14,148,953 (10,288,299) 11,567,522 (8,413,380–16,775,460)	<i>n</i> = 25 19,292,839 (11,273,771) 16,304,813 (11,766,696–19,211,896)
Annual total healthcare expenditures	<i>n</i> = 176 9,677,834.0 (6,012,843.2) 9,357,499 (5,132,374–12,903,367)	<i>n</i> = 106 6,432,047.3 (4,747,105.5) 5,754,848 (2,783,794–9,355,226)	<i>n</i> = 142 7,697,124.3 (5,482,313.4) 7,178,041 (3,842,297–11,645,462)	<i>n</i> = 152 9,277,684.2 (6,491,457.7) 8,954,297 (4,502,050–12,729,419)	<i>n</i> = 157 11,820,286 (8,412,358.2) 10,805,342 (6,271,350–15,695,433)	<i>n</i> = 134 15,652,288 (10,036,831) 14,372,416 (9,757,270–17,983,315)
Aged 12–19 years						
Annual expenditures for CFC and emicizumab treatment	<i>n</i> = 106 15,281,996 (8,610,391.1) 15,851,293 (9,158,305–19,557,253)	<i>n</i> = 64 13,093,183 (8,124,292.6) 11,502,828 (7,620,215–18,349,905)	<i>n</i> = 83 13,951,222 (8,430,164.4) 13,314,780 (7,219,050–18,797,597)	<i>n</i> = 80 15,848,284 (10,163,167) 15,138,938 (8,863,208–20,403,907)	<i>n</i> = 82 18,764,547 (10,749,027) 18,693,798 (12,502,992–25,151,463)	<i>n</i> = 72 19,851,703 (14,894,727) 17,518,440 (8,105,716–25,658,444)

Continued

Annual expenditures for CFC treatment	<i>n</i> = 103 13,793,120 (7,359,192.7) 14,717,088 (8,453,820–18,288,759)	<i>n</i> = 63 13,107,956 (8,188,682.5) 11,327,573 (7,566,752–19,021,095)	<i>n</i> = 82 14,095,687 (8,378,032.6) 13,463,550 (7,753,920–18,797,597)	<i>n</i> = 79 15,869,318 (10,226,355) 15,227,050 (8,589,350–20,578,118)	<i>n</i> = 79 16,695,171 (8,611,804.1) 16,910,940 (11,898,850–22,245,338)	<i>n</i> = 59 14,049,361 (8,192,377.9) 14,037,008 (7,521,248–19,364,692)
Annual expenditures for emicizumab treatment	<i>n</i> = 5 40,303,143 (8,046,233.2) 40,571,263 (35,661,527–40,740,843)	<i>n</i> = 0 – –	<i>n</i> = 0 – –	<i>n</i> = 1 14,186,557 (–) 14,186,557 (14,186,557–14,186,557)	<i>n</i> = 5 35,245,523 (10,523,473) 34,796,314 (29,919,696–44,714,987)	<i>n</i> = 5 48,835,632 (8,764,836.3) 50,532,531 (46,685,372–51,222,830)
Annual total healthcare expenditures	<i>n</i> = 106 16,323,213 (9,003,118.1) 16,841,200 (9,545,931–21,212,583)	<i>n</i> = 64 13,597,021 (8,107,822.7) 12,738,293 (8,098,371–18,418,050)	<i>n</i> = 83 15,715,736 (8,489,767.2) 15,070,840 (9,996,275–21,513,254)	<i>n</i> = 80 17,223,526 (10,731,561) 15,911,990 (10,145,170–21,190,415)	<i>n</i> = 82 19,209,825 (11,009,594) 18,776,573 (12,572,372–25,676,233)	<i>n</i> = 72 21,314,042 (14,479,892) 19,001,069 (10,664,144–26,282,585)

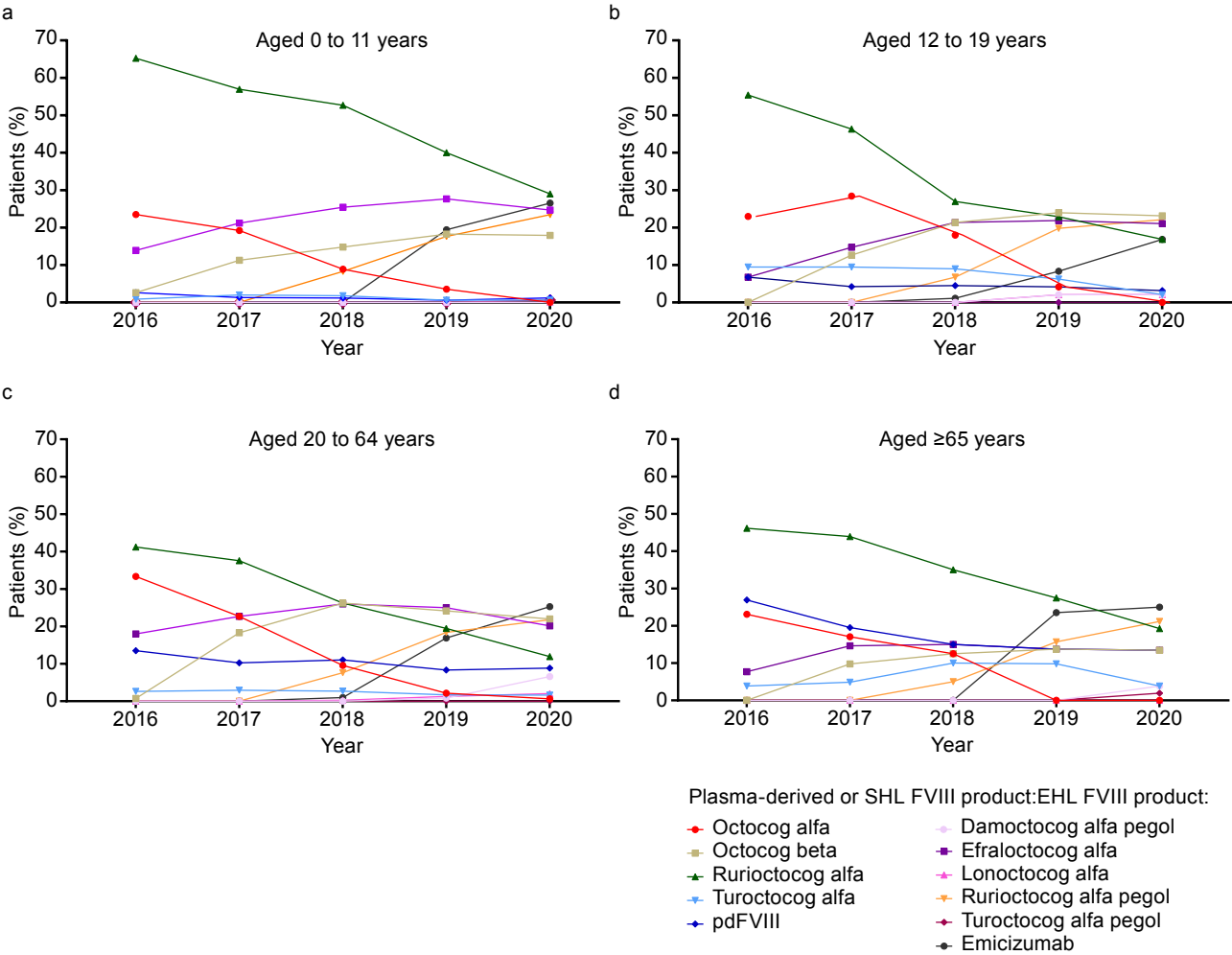
Aged 20–64 years

Annual expenditures for CFC and emicizumab treatment	<i>n</i> = 477 17,006,119 (12,266,866) 15,280,218 (7,502,612–23,689,039)	<i>n</i> = 242 11,763,338 (9,493,366.8) 9,937,186 (4,670,580–16,033,080)	<i>n</i> = 360 11,914,527 (9,488,770.4) 9,718,422 (4,934,950–16,615,958)	<i>n</i> = 336 14,142,404 (10,487,480) 12,563,831 (5,978,214–19,849,715)	<i>n</i> = 405 21,186,119 (16,271,380) 17,628,512 (8,420,905–28,542,320)	<i>n</i> = 392 25,945,730 (18,456,422) 22,158,154 (11,233,781–36,744,898)
Annual expenditures for CFC treatment	<i>n</i> = 462 13,102,651 (9,306,869.3) 11,766,172 (5,798,181–18,569,662)	<i>n</i> = 242 11,763,338 (9,493,366.8) 9,937,186 (4,670,580–16,033,080)	<i>n</i> = 359 11,940,875 (9,488,816.4) 9,721,893 (4,938,505–16,728,796)	<i>n</i> = 334 13,936,458 (10,072,758) 12,409,564 (5,903,660–19,819,780)	<i>n</i> = 376 15,458,345 (11,308,235) 13,299,158 (6,715,159–22,805,401)	<i>n</i> = 327 16,203,214 (11,818,473) 15,002,162 (6,417,000–23,510,047)
Annual expenditures for emicizumab treatment	<i>n</i> = 68 44,418,244 (11,557,115) 41,812,657 (37,207,596–50,371,545)	<i>n</i> = 0 – –	<i>n</i> = 0 – –	<i>n</i> = 3 29,905,357 (15,402,341) 37,873,856 (12,151,236–39,690,980)	<i>n</i> = 67 38,548,089 (15,775,067) 34,887,979 (27,023,058–49,167,086)	<i>n</i> = 67 51,033,097 (13,366,999) 51,283,296 (42,954,576–58,444,480)

Annual total healthcare expenditures	<i>n</i> = 477 18,446,448 (12,711,999) 16,992,630 (8,550,291– 26,152,229)	<i>n</i> = 242 12,837,970 (10,279,220) 10,529,485 (5,387,536– 17,320,449)	<i>n</i> = 360 13,796,872 (10,046,141) 11,561,370 (6,162,817– 20,559,511)	<i>n</i> = 336 15,706,867 (11,099,998) 13,962,846 (6,891,543– 21,585,038)	<i>n</i> = 405 22,509,394 (16,656,189) 18,759,533 (9,852,950– 30,955,980)	<i>n</i> = 392 27,491,007 (18,476,460) 23,891,307 (12,482,901– 39,144,803)
Aged ≥65 years						
Annual expenditures for CFC and emicizumab treatment	<i>n</i> = 53 12,730,484 (11,619,675) 11,152,208 (2,732,709– 19,372,238)	<i>n</i> = 23 7,846,759.3 (6,031,441.9) 5,072,292 (3,039,080– 12,541,900)	<i>n</i> = 36 6,882,466.8 (5,948,545.5) 5,429,056 (1,954,814– 9,326,753)	<i>n</i> = 32 8,451,415.2 (6,737,948.7) 6,281,372 (2,697,128– 12,655,064)	<i>n</i> = 43 17,502,524 (16,069,083) 14,287,120 (4,918,062– 29,030,867)	<i>n</i> = 39 19,098,758 (16,882,030) 14,982,468 (3,414,765– 34,316,532)
Annual expenditures for CFC treatment	<i>n</i> = 50 8,713,027.1 (7,143,725.9) 6,704,601 (2,716,515– 12,487,678)	<i>n</i> = 23 7,846,759.3 (6,031,441.9) 5,072,292 (3,039,080– 12,541,900)	<i>n</i> = 36 6,882,466.8 (5,948,545.5) 5,429,056 (1,954,814– 9,326,753)	<i>n</i> = 31 8,646,022.9 (6,757,290.8) 6,575,381 (2,975,680– 13,253,100)	<i>n</i> = 38 9,396,188.8 (7,994,099.4) 6,722,838 (2,144,922– 15,483,732)	<i>n</i> = 30 10,546,029 (9,695,651.1) 7,350,466 (2,191,072– 17,406,608)
Annual expenditures for emicizumab treatment	<i>n</i> = 10 39,348,703 (9,284,421.9) 35,795,497 (30,991,779– 47,996,393)	<i>n</i> = 0 – – –	<i>n</i> = 0 – – –	<i>n</i> = 0 – – –	<i>n</i> = 10 37,168,244 (14,306,967) 34,938,806 (28,295,904– 43,680,364)	<i>n</i> = 10 41,529,163 (9,893,746.7) 40,818,225 (33,687,654– 44,488,330)
Annual total healthcare expenditures	<i>n</i> = 53 15,107,960 (12,247,289) 13,286,602 (4,734,360– 22,793,931)	<i>n</i> = 23 9,511,329.3 (6,370,949.3) 8,719,797 (4,751,539– 15,124,262)	<i>n</i> = 36 9,365,499.0 (7,528,276.9) 8,103,974 (2,608,955– 14,947,614)	<i>n</i> = 32 11,554,559 (8,631,324.8) 10,001,373 (4,480,340– 17,815,047)	<i>n</i> = 43 20,232,780 (17,315,738) 17,474,568 (5,311,624– 32,671,880)	<i>n</i> = 39 22,323,561 (16,724,176) 18,963,319 (5,786,937– 37,166,753)

CFC clotting factor concentrate, *Q* quartile

Fig. S1 Outpatient use of treatments for hemophilia A by age: **(A)** 0–11 years, **(B)** 12–19 years, **(C)** 20–64 years, and **(D)** ≥65 years



EHL extended half-life, FVIII factor VIII, pd plasma-derived factor VIII, SHL standard half-life